REMARKS

Following entry of this amendment, claims 1-5, 7, 9-19, and 21-25 are pending in the application. The amendment to claims 1 and 10 merely clarifies that metastasis occurs in the animal's own bone. The amendment to claim 18 merely clarifies that the antibody is derived from a mouse. The amendments to claims 24 and 25 merely reflect more common method claim structure. Accordingly, none of these amendments alter the scope of these claims.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 18, 24, and 25 under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out an distinctly claim the subject matter which applicant regards as the invention." Action at page 2. The Examiner asserted that "[c]laim 18 is vague and indefinite because of the claim recitation 'mouse antibody.' It is unclear [whether] the phrase embraces an antibody against a mouse antigen or an antibody made in the mouse, thus, the metes and bounds of the claim is unclear." *Id.*

Solely to expedite prosecution and without acquiescing to the rejection, Applicants have amended claim 18 to recite "[t]he method according to claim 16, wherein the antibody is derived from a mouse." This amendment merely clarifies the claim without altering its scope. Applicants assert that amended claim 18 is definite under 25 U.S.C. § 112, second paragraph.

The Examiner further alleged that claims 24 and 25 are incomplete because "there is no step or conclusion to indicate how the efficiency of the treatment or the

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effect of the test substance is determined, which would clearly relate back to the preamble." Action at page 3.

Solely to expedite prosecution and without acquiescing to the rejection, Applicants have amended claim 24 to further recite "thereby evaluating the efficiency of the treatment against bone metastasis of tumor cells" and have amended claim 25 to further recite "thereby determining the effect of the test substance on bone metastasis." Applicants assert that amended claims 24 and 25 now contain conclusions that clearly relate back to the preamble.

In view of the foregoing amendments, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-5, 7, 9-19, and 21-25 under 35 U.S.C. § 112, first paragraph, for lack of enablement, alleging that the specification "does not reasonably provide enablement for producing any rodent bone metastasis model animal by *any* peripheral administration of *any* cancer or tumor cells in *any* immunodeficient rodents." Action at page 3. The Examiner further asserted that "the applicant was not successful in creating such a metastatic model with any human lung cancer cells, let alone other cancer cell types." Action at page 4. Applicants respectfully traverse.

At the outset, however, Applicants bring to the attention of the Examiner what must have been an inadvertent omission. Specifically, the Examiner alleged that the

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level of skill in the art at the time of filing is represented by Folstad et al., *J. Cell. Biochem.*, 56: 23-28 (1994) (Folstad), and then quoted Folstad as stating that:

> '[i]mmunodeficient nude and SCID mice, as well as nude rats, provide important tools for tumor biology research. One major drawback has been the very low frequency of spontaneous metastasis observed when human tumors are grown subcutaneously in such rodents', 'The health status of the animals, the nature of their immunodecificiency, the preparation of tumor material, and the site or route of cell administration seem to have a strong impact on both the development of metastatic tumor lesions and on the pattern of metastasis' (right column, page 23).

Id.

In fact, the passage in Folstad stands for the opposite proposition, i.e., that researchers have been successfully developing models for spontaneous human tumor metastasis "during the last decade." This position is set forth in an intervening sentence which was omitted from the Examiner's quote. This omitted sentence reads "[h]owever, during the last decade an increasing number of investigators have reported on models for spontaneous and experimental human tumor metastasis." Folstad at page 23, right column. Moreover, Folstad was published in 1994, seven years before the filing date of the instant application. Thus, for at least 17 years prior to the filing date of the application, an increasing number of researchers have been successfully producing animal models for human tumor metastasis. This full quote undercuts entirely the Examiner's premise of lack of success in this effort and supports Applicants' contention that the level of skill in the art of human tumor metastasis model animals was actually high at the time of filing.

As to the enablement provided in the specification, peripheral administration is fully enabled. The specification provides that peripheral administration includes "intravenous, intramuscle, intracutaneous, subcutaneous, and intraperitoneal

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administration." Specification at page 8. Each of these methods of administration was well known in the art at the time of filing, so the application is clearly enabled with respect to peripheral administration.

Furthermore, Applicants point out that the claims do not recite "*any* cancer or tumor cells." Instead, the claims recite "tumor cells that induce bone metastasis," and the specification fully enables use of these cells as well as methods to determine which tumor cells actually did induce bone metastasis. For example, the specification expressly teaches at least one criterion for selecting such tumor cells, stating that "it was reported that PTHrP-expression in primary tumors directly correlated with the incidence of bone metastasis in breast cancer patients." Specification at page 11. The specification also notes that "[c]onsistent with the formation of bone metastasis by SBC-5 cells, the levels of PTHrP and calcium in the mouse serum were increased in a time-dependent manner, suggesting that PTHrP produced by human lung cancer may play a crucial role in the formation of bone metastasis and hypercalcemia." Specification at page 2. Thus, the specification provides a method for identifying tumor cells that cause bone metastasis in model animals and also provides guidance in selecting likely candidate tumor cells. Accordingly, one skilled in the art would be able to identify tumor cells for use in the bone metastasis model animals without undue experimentation.

Finally, as discussed in the Amendment and Response filed July 15, 2002, the specification enables the use of immunodeficient rodents. The specification indicates that "[a]nimals which belong to rodents, for example, mouse, rat, hamster, and the like, are preferably used in the present invention." Specification at page 8. In addition to mice, one skilled in the art would be able to use the teachings of the specification to make, e.g., a rat bone metastasis model animal. Nude rats were well known in the art

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at the time of filing and were known to be immunodeficient and useful as tumor metastasis model animals. See, e.g., Mundy et al., *Seminars in Oncol.*, 28: 35-44 (2001) (cited by the Examiner in the Office Action mailed January 16, 2002; hereafter "Mundy"). One skilled in the art would have been able to apply the teachings of the specification to rats. For instance, the specification teaches that a "nude mouse which is deficient of T cell function due to lack of thymus...is used as a immunodeficient model for implanting tumor." Specification at pages 8 and 9. One skilled in the art would be able to use a nude rat, which also lacks a thymus and is immunodeficient, in place of the nude mouse without undue experimentation. The specification teaches introduction of the tumor cells peripherally, and evaluation of bone metastases, e.g., by X-ray photography. Peripheral administration and x-ray photography were both known in the art and used on rats at the time the application was filed. Therefore, the specification enables the use of not only mice, but other rodents such as rats, in the claimed bone metastasis model.

In view of the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-5, 7, 9-19, and 21-25 under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 102

The Examiner maintained the rejection of claims 1, 3-10, 12, and 19-25 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,643,551 (hereafter "Namikawa"). The Examiner asserted that "the limitation of colonization in [the rodent's] own bone tissue is not present in the claims. Therefore *Namikawa et al* teach all the elements of the claims, and the rejection stands." Action at page 5. Applicants note

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that claims 6, 8, and 20 were canceled in the Amendment and Response filed July 15, 2002. Applicants will therefore consider the rejection as to claims 1, 3-5, 7, 9-10, 19, and 21-25.

Solely to expedite prosecution, and without acquiescing to the rejection, Applicants have amended claims 1 and 10. Thus, claim 1 now recites "wherein the metastasis occurs in the animal's own bone," and claim 10 now recites "wherein the metastasis occurs in the animal's own bone." Claims 3-5, 7, and 9 ultimately depend from claim 1 and claims 19 and 21-23 ultimately depend from claim 10. Claims 24 and 25 each recite "the rodent bone metastasis model animal according to any one of claims 1 to 5, 7, or 9," and therefore also ultimately inherit the recitation "wherein the metastasis occurs in the animal's own bone" from claim 1.

As discussed in the Amendment and Response filed July 15, 2002, Namikawa requires the prior introduction of viable human tissue, which is then colonized by the subsequently introduced human metastatic cells. Namikawa does not obtain metastasis to the animal's own bone. Thus, Namikawa does not anticipate claims 1, 3-5, 7, 9-10, 19, and 21-25 because Namikawa does not teach a rodent bone metastasis model animal, wherein the metastasis occurs in the animal's own bone.

In view of the foregoing amendments and discussion, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 3-5, 7, 9-10, 19, and 21-25 under 35 U.S.C. § 102(b) over Namikawa.

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The Examiner rejected claims 1-5, 7, 9-19, and 21-25 under 35 U.S.C. § 102(b) as allegedly being anticipated by Miki et al., *Oncol. Res.* 12(5): 209-217 (2000) (hereafter "Miki").[1] Action at page 6.

Applicants assert that Miki was improperly cited against the instant application. Although Miki appears to be a 2000 publication, it was not published until June 14, 2001, and was not available to the public before that date. See attached Declaration Under 37 C.F.R. § 1.132. The filing date of the instant application is May 25, 2001, which is before the publication date of Miki. Accordingly, Miki may not be used as prior art against the application, and the rejection of claims 1-5, 7, 9-19, and 21-25 under 35 U.S.C. § 102(b) over Miki is improper and should be withdrawn.

The Examiner rejected claims 1, 2, 4, 5, 10, 11, 24, and 25 under 35 U.S.C. § 102(b) as allegedly being anticipated by Engebraaten et al., *Int. J. Cancer*, 82: 219-225 (1999) (hereafter "Engebraaten"). Action at page 6. The Examiner argued that "*Engebraaten et al* teach establishing a nude rat model for bone metastasis using human breast cancer cells MT-1 by intracardial injection, which exhibited consistent bone/bone marrow metastases in addition to brain and spinal cord tumors." *Id.*

Applicants respectfully traverse. In order to anticipate a claim, a reference must teach each and every element of that claim. Claim 1 recites "[a] rodent bone metastasis model animal exhibiting bone metastasis of tumor cells, *in which tumor cells that induce bone metastasis have been introduced by peripheral administration*, wherein the animal

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[1] Miki was accepted for publication on December 20, 2000, which is less than one year before the filing date of the instant application, May 21, 2001. Thus, Miki is not § 102(b) prior art against the application. (In fact, Miki is not prior art at all, because it was published much later, on June 14, 2001.)

is immunodeficient, and wherein the metastasis occurs in the animal's own bone." (Emphasis added.) Peripheral administration includes " intravenous, intramuscle, intracutaneous, subcutaneous, and intraperitoneal administration." Specification at page 8. In Engebraaten, the only instance in which the authors obtained bone metastases was following intracardial injection of MT-1 cells. Thus, Engebraaten does not teach a bone metastasis model in which tumor cells that induce the bone metastasis were introduced by peripheral administration and cannot teach every element of claim 1. Claims 2, 4, 5, 24, and 25 ultimately depend from claim 1 and are therefore also not anticipated by Engebraaten.

Claim 10 recites, in part, "introducing tumor cells that induce bone metastasis into the animal by peripheral administration." Thus, for at least the reasons discussed above for claim 1, Engebraaten also does not teach every element of claim 10 and therefore does not anticipate that claim. Furthermore, claim 11 depends from claim 10 and is therefore also not anticipated by Engebraaten.

Since Applicants have shown that Engebraaten fails to teach every limitation of the claims, Applicants need not address the Examiner's other contentions such as, for example, the statement that that the "claim recitation 'highly expressing PTHrP' has not been given patentable weight in determining the novelty of the invention in this rejection." Action at page 6. By not addressing those contentions, Applicants in no way acquiesce to those contentions. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2, 4, 5, 10, 11, 24, and 25 under 35 U.S.C. § 102(b) over Engebraaten.

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The Examiner rejected claims 1, 4, 5, 7, 9, 10, 13-15, and 21-25 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,365,797 (hereafter "Sawyers"). The Examiner alleged that Sawyers teaches:

> establishing a SCID mouse model for bone metastasis using human prostate cancer LAPC-4 cells by subcutaneous injection, which exhibited consistent bone/bone marrow metastases in addition to lymph and pulmonary metastasis tumors, wherein an enhanced frequency of bone metastasis was observed in a subset of the mice pretreated with a combination of radiation and NK cell depletion (column 24, lines 31-35)."

Action at page 7.

Applicants respectfully traverse. Sawyers does not teach *peripheral* injection tumor *cells* to produce bone metastases which are specific elements of the pending claims. As discussed above, claim 1 recites "[a] rodent bone metastasis model animal exhibiting bone metastasis of tumor cells, in which tumor cells that induce bone metastasis have been introduced by peripheral administration, wherein the animal is immunodeficient, and wherein the metastasis occurs in the animal's own bone." Claim 10 recites in part "introducing tumor cells that induce bone metastasis into the animal by peripheral injection." Thus, claims 1 and 10 recite the peripheral injection of tumor *cells*.

Sawyers, on the other hand, teaches "an immune deficient mouse having a human prostate xenograft of locally advanced or metastatic prostate cancer and uses thereof." Sawyers at Abstract. Sawyers implants 2-3 mm^3 sections of human prostate cancer *biopsy tissue*. *See*, e.g., Sawyers at column 15, lines 35-40. Sawyers itself distinguishes between the use of biopsy tissue and the use of cell suspensions in various experiments. Moreover, in instances where Sawyers discusses injection of single cell suspensions of prostate cancer cells, the suspensions are injected directly into the bone marrow or directly into the prostate, i.e., they are not injected peripherally.

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Thus, Sawyers does not anticipate the claims 1 and 10 because Sawyers does not teach *peripheral* injection tumor *cells* to produce bone metastases.

Claims 4, 5, 7, 9, 24, and 25 ultimately depend from claim 1 and claims 13-15 and 21-23 ultimately depend from claim 10, so for at least the reasons discussed above, applicants assert that those claims are also not anticipated by Sawyers.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 4, 5, 7, 9, 10, 13-15, and 21-25 under 35 U.S.C. § 102(e) over Sawyers.

Rejections Under 35 U.S.C. § 103 (a)

The Examiner maintained the rejection of claims 2, 11, and 13-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Namikawa in view of Yano et al., *Intl. J. Cancer*, 67: 211-217 (1996) (hereafter "Yano") and Mundy. Action at page 8. The Examiner asserted that Yano teaches NK cell depletion and Mundy teaches PTHrP-expressing breast cancer cells. Applicants respectfully traverse because the Examiner has not set forth a *prima facie* case of obviousness.

Indeed, the Examiner has not set forth any motivation to combine the references. Instead, the Examiner merely alleges that "the test [for obviousness] is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981)." Action at page 8. In fact, the Office is obligated to present a factual showing of the teaching or motivation to combine references. As the Federal Circuit reiterated in reversing the Board of Appeals in *In re Lee*, 277 F.3d 1338, 61 USPQ2d 1430 (2002):

> Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the

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> requirement for a showing of the teaching or motivation to combine prior art references. . . . This precedent has been reinforced in myriad decisions, and cannot be dispensed with.

Id. at 1343. Thus, the Examiner must identify the specific motivation for combining Namikawa, Yano, and Mundy to suggest a bone metastasis model in which peripherally injected human tumor cells metastasize to the animal's own bone.

As discussed above, these elements have been added to the claims solely to expedite prosecution and without acquiescing to the rejection. Specifically, claims 1 and 10 have been amended to recite "wherein the metastasis occurs in the animal's own bone." Claim 2 depends from claim 1 and claims 13-18 each ultimately depend from claim 10. For the reasons discussed above and in the Amendment and Response filed July 15, 2002, Namikawa fails to teach a rodent bone metastasis model animal wherein the metastasis occurs in the animal's own bone.

Moreover, Namikawa in fact teaches away from the claimed invention, because Namikawa obtains only tumor metastases in human bone xenografts, and not in the animal's own bone. Thus, one skilled in the art would not reasonably expect success at obtaining metastasis to the animal's own bone using the method of Namikawa.

Yano fails to remedy this deficiency of Namikawa. Yano discusses a mouse metastasis model in which metastasis occurs in the lymph nodes, liver, and kidneys. Out of about 67 mice that were intravenously injected with tumor cells, Yano failed to obtain a single bone metastasis. Thus, not only does Yano teach away from the invention, but it also would not have provided any reasonable expectation of success of producing a bone metastasis in the animal's own bone by intravenous injection.

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Finally, Mundy also fails to remedy the deficiencies of Namikawa alone or with Yano. Mundy discusses a number of animal models for bone metastasis, but none of those models involve the peripheral administration of human tumor cells that results in metastasis to the animal's own bone. Specifically, Mundy only discusses inoculation of human tumor cells into the left cardiac ventricle (see, e.g., Mundy at page 38, right column, second paragraph), or direct inoculation of human tumor cells into bone (see, e.g., Mundy at page 39, left column, first paragraph). Thus, Mundy also fails to demonstrate that peripheral injection of tumor cells results in bone metastasis occurring in the animal's own bone, and therefore also does not remedy the deficiencies of Namikawa.

Accordingly, the primary and secondary references either demonstrate that peripheral injection of human tumor cells fails to produce metastasis to the animal's own bone (Namikawa and Yano) or that human tumor cells must be injected directly into the bone or into the left cardiac ventricle to obtain bone metastases (Mundy). Thus, there is no motivation to combine these references and certainly no reasonable expectation of success that the combination of references would produce a bone metastasis model animal in which *peripherally* injected human tumor cells metastasize to the *animal's own bone*.

For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 2, 11, and 13-18 under 35 U.S.C. § 103(a) over Namikawa in view of Yano and Mundy.

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The Examiner rejected claims 10 and 16-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sawyers in view of Yano. Action at page 9. The

Examiner asserted that Sawyers teaches "establishing a SCID mouse model for bone metastasis using human prostate cancer LAPC-4 cells by subcutaneous injection...wherein an enhanced frequency of bone metastasis was observed in a subset of the mice pretreated with a combination of radiation and NK cell depletion." *Id.* The Examiner further alleged that, while Sawyers does not teach how NK-depletion is achieved, Yano remedies that deficiency by teaching pre-treatment with an anti-mouse IL-2 receptor beta chain antibody. *Id.* Applicants respectfully traverse.

As discussed above, claim 10 recites

> [a] method for producing a rodent exhibiting bone metastasis of tumor cells, comprising:
> (i) providing a rodent having reduced immunity; and
> (ii) introducing tumor cells that induce bone metastasis into the animal by peripheral administration, wherein the metastasis occurs in the animal's own bone.

Claims 16-18 ultimately depend from claim 10. Also as discussed above, Sawyers fails to teach a method for producing a rodent exhibiting bone metastasis in which peripherally injected human tumor cells metastasize to the animal's own bone. Briefly, Sawyers discusses only implantation of human prostate cancer *biopsy tissue*, and does not discuss peripheral injection of human tumor *cells*. This distinction is recognized in Sawyers, as the authors conducted separate experiments involving implantation of human cancer biopsy tissue or injection of human tumor cells. Importantly, the authors only injected human tumor cells directly into the prostate or bone of the model animal, and not peripherally. Thus, Sawyers fails to teach a method of producing a bone metastasis model animal by peripheral injection of human tumor cells that metastasize to the animal's own bone.

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For all the reasons set forth above, Yano would not have remedied those deficiencies. Accordingly, Applicants need not and will not address the merits of the Examiner's arguments concerning Yano with respect to NK cell depletion, and this should not be construed as any acquiescence to those arguments.

Since claims 16-18 ultimately depend from claim 10, for at least this reason, the Examiner has failed to establish that claims 16-18 would have been obvious over Sawyers in view of Yano. As above and also without acquiescence, Applicants need not and will not address any of the Examiner's other contentions.

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 10 and 16-18 under 35 U.S.C. § 103(a) over Sawyers in view of Yano.

Applicants respectfully assert that the present application is in condition for allowance and request that the Examiner issue a timely Notice of Allowance for pending claims 1-5, 7, 9-19, and 21-25. If the Examiner does not consider the application to be allowable, the undersigned requests that, prior to taking action, the Examiner call her at (650) 849-6656 to set up an interview.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: March 20, 2003

By: _____
Rebecca B. Scarr
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APPENDIX TO AMENDMENT

Version with Markings to Show Changes Made

IN THE CLAIMS:

Changes made to claims 1, 10, 18, 24, and 25:

1. (Twice amended) A rodent bone metastasis model animal exhibiting bone metastasis of tumor cells, in which tumor cells that induce bone metastasis have been introduced by peripheral administration, [and] wherein the animal is immunodeficient, and wherein the metastasis occurs in the animal's own bone.

10. (Twice amended) A method for producing a rodent exhibiting bone metastasis of tumor cells, comprising:

(i) providing [a] an immunodeficient rodent [having reduced immunity]; and

(ii) introducing tumor cells that induce bone metastasis into the animal by peripheral administration, wherein the metastasis occurs in the animal's own bone.

18. (Amended) The method according to claim 16, wherein the antibody is [a mouse antibody] derived from a mouse.

24. (Twice amended) A method for evaluating efficiencies of treatment against bone metastasis of tumor cells, comprising:

(i) applying a treatment to the rodent bone metastasis model animal according to any one of claims 1 to 5, 7, or 9; and

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(ii) comparing the size and/or extent of bone metastasis, and/or symptoms [resulted] resulting from bone metastasis, with a control animal; thereby evaluating the efficiency of the treatment against bone metastasis of tumor cells.

25. (Twice amended) A method for determining the effect of a test substance on bone metastasis, comprising:

(i) administering the test substance to the rodent bone metastasis model animal according to any of claims 1 to 5, 7, or 9; and

(ii) comparing the size and/or extent of bone metastasis, and/or symptoms [resulted] resulting from bone metastasis, with a control animal; thereby determining the effect of the test substance on bone metastasis.

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